Intravitreal Sirolimus for Noninfectious Uveitis: A Phase III Sirolimus Study Assessing Double-masked Uveitis Treatment (SAKURA)

Quan Dong Nguyen, MD, MSc,1 Pauline T. Merrill, MD,2 W. Lloyd Clark, MD,3 Alay S. Banker, MD,4 Christine Fardeau, MD,5 Pablo Franco, MD,6 Phuc LeHoang, MD, PhD,5 Shigeaki Ohno, MD, PhD,7 Sivakumar R. Rathinam, FAMS, PhD,8 Stephan Thurau, MD, FEBO,9 Abu Abraham, MD,10 Laura Wilson, MD,11 Yang Yang, PhD,11 Naveed Shams, MD, PhD,10 for the Sirolimus study Assessing double-masked Uveitis Treatment (SAKURA) Study Group*

Purpose: To evaluate the efficacy and safety of intravitreal sirolimus in the treatment of noninfectious uveitis (NIU) of the posterior segment (i.e., posterior, intermediate, or panuveitis).

Design: Phase III, randomized, double-masked, active-controlled, 6-month study with intravitreal sirolimus.

Participants: Adults with active NIU of the posterior segment (intermediate, posterior, or panuveitis), defined as a vitreous haze (VH) score >1+. Subjects discontinued NIU medications before baseline, except for systemic corticosteroids, which were allowed only for those already receiving them at baseline and were rapidly tapered after baseline per protocol.

Methods: Intravitreal sirolimus assigned 1:1:1 at doses of 44 (active control), 440, or 880 μg, administered on Days 1, 60, and 120.

Main Outcome Measures: The primary efficacy outcome was the percentage of subjects with VH 0 response at Month 5 (study eye) without use of rescue therapy. Secondary outcomes at Month 5 were VH 0 or 0.5+ response rate, corticosteroid tapering success rate (i.e., tapering to a prednisone-equivalent dosage of ≤5 mg/day), and changes in best-corrected visual acuity (BCVA). Adverse events during the double-masked treatment period are presented.

Results: A total of 347 subjects were randomized. Higher proportions of subjects in the intravitreal sirolimus 440 μg (22.8%; P = 0.025) and 880 μg (16.4%; P = 0.182) groups met the primary end point than in the 44 μg group (10.3%). Likewise, higher proportions of subjects in the 440 μg (52.6%; P = 0.008) and 880 μg (43.1%; P = 0.228) groups achieved a VH score of 0 or 0.5+ than in the 44 μg group (35.0%). Mean BCVA was maintained throughout the study in each dose group, and the majority of subjects receiving corticosteroids at baseline successfully tapered off corticosteroids (44 μg [63.6%], 440 μg [76.9%], and 880 μg [66.7%]). Adverse events in the treatment and active control groups were similar in incidence, and all doses were well tolerated.

Conclusions: Intravitreal sirolimus 440 μg demonstrated a significant improvement in ocular inflammation with preservation of BCVA in subjects with active NIU of the posterior segment. Ophthalmology 2016;123:2413-2423 © 2016 by the American Academy of Ophthalmology

*Supplemental material is available at www.aaojournal.org.
common, patients referred to a uveitis specialist are more likely to have involvement of the posterior segment. In a cross-sectional, multicenter study of 580 patients with noninfectious uveitis (NIU) in the United States, the percentages by anatomic site were intermediate, 24%; posterior, 26%; panuveitis, 21%; and anterior, 29%. The pathophysiology of NIU is often autoimmune, manifesting secondary to systemic diseases (e.g., Behçet’s disease, sarcoidosis, Vogt–Koyanagi–Harada syndrome) or due to local conditions (e.g., punctate inner choroidopathy, birdshot chorioretinopathy, multifocal choroiditis, and serpiginous chorioretinopathy). A substantial proportion of cases are described as idiopathic or undifferentiated.13,14

Inflammation of the uvea and adjacent structures in NIU is mediated by T cells and perpetuated by proinflammatory cytokines. Accordingly, treatments used in NIU (e.g., systemic and local corticosteroids, systemic immunosuppressants, and biologics) target the inflammatory pathology.15 Systemic corticosteroids, except in contraindicated or refractory cases, are effective in a majority of patients.12,16,17 Nonetheless, the long-term use of systemic corticosteroids is associated with a risk of serious adverse effects, such as insulin-dependent diabetes mellitus, myopathy, and pancreatitis.18 Although uveitis treatment guidelines recommend chronic systemic corticosteroid use at no more than 10 mg/day prednisone-equivalent dose to minimize the potential for serious adverse events,16 even dosages as low as 7.5 mg/day have been shown to be associated with adverse outcomes.12 Local, topical or injected/implanted corticosteroids may not be effective in all forms of NIU and carry the risk of adverse ocular effects, such as elevated intraocular pressure (IOP), glaucoma, and cataract.17–19

Sirolimus is an immunoregulatory agent that inhibits the activity of the serine/threonine protein kinase mammalian target of rapamycin (mTOR).20 The mTOR pathway plays a critical role in autoimmune inflammation, promoting the activation, proliferation, and differentiation of T cells, and producing inflammatory cytokines.21 Sirolimus inhibits mTOR activity, thereby suppressing the lymphocyte response to interleukin-2 while promoting regulatory T-cell development and function.22 Oral administration of sirolimus demonstrated complete inhibition of autoimmune uveitis in preclinical models23,24 and was also effective in patients with severe NIU.22 However, oral sirolimus requires laboratory and clinical monitoring for systemic toxicity.24 An intravitreal formulation of sirolimus (DE-109) has recently been developed and shown to deliver the drug efficiently to the retina/choroid, with negligible systemic exposure.25 Intravitreal sirolimus appeared to be effective in reducing ocular inflammation in subjects with active or quiescent NIU in the Phase I Sirolimus as a therapeutic Approach for uVeitis (SAVE) study.26,27 On the basis of results from the SAVE study and preliminary results from the ongoing SAVE-2 study, a Phase III, multicenter, randomized, double-masked study, the Sirolimus study Assessing double-masKed Uveitis tReAtment (SAKURA) Study 1 was initiated to assess the efficacy and safety of intravitreal sirolimus in subjects with active NIU of the posterior segment.

**Methods**

**Study Design**

The SAKURA Study 1 is the first of 2 Phase III, randomized, double-masked, multinational studies conducted in the European Union, India, Israel, Japan, Latin America, and the United States. Both studies are registered at ClinicalTrials.gov (NCT01358266). Subjects randomized up to March 31, 2013 comprise the population of SAKURA Study 1, and subjects enrolling from April 1, 2013 were randomized into SAKURA Study 2 (ongoing).

SAKURA Study 1 consists of a 6-month double-masked treatment period, followed by a 6-month open-label treatment period and a 12-month re-treatment period during which eligible subjects were to receive 880-µg injections. The results from the double-masked treatment period of SAKURA Study 1 are reported here.

Subject eligibility criteria included age ≥18 years; an investigator-determined diagnosis of active NIU of the posterior segment (which in this study includes intermediate, posterior, or panuveitis), defined as a vitreous haze (VH) score of >1+ in the study eye; and a best-corrected visual acuity (BCVA) of 10/20 or better in the fellow eye. If an anterior component of uveitis was present, it had to be less than the posterior component. Key ocular exclusion criteria included active infectious uveitis, a primary diagnosis of anterior uveitis, uncontrolled glaucoma as evidenced by an IOP >21 mmHg while on medical therapy, use of intravitreal injections or posterior subtenon corticosteroids 90 days before baseline, or a history of vitrectomy in the study eye.

After a 30-day screening period, subjects were randomized at baseline in a 1:1:1 ratio to intravitreal sirolimus 44, 440, or 880 µg, all administered via a 20 µl injection in the study eye on Days 1, 60, and 120 (Fig 1). The 440 µg dose was selected on the basis of the efficacy and tolerability of a comparable dose used in the Phase I SAVE study,27 whereas the 44 and 880 µg doses were selected on the basis of preclinical pharmacology findings (as well as formulation requirements). In subjects with bilateral disease, the eye with a greater VH score on Day 1 was selected to be the study eye. If the VH scores were equal in both eyes, the right eye was chosen as the study eye. Details of randomization and masking are described in the Supplementary Appendix (available at www.aaojournal.org).

To assess the treatment effects of intravitreal sirolimus, treatment with immunosuppressive therapy other than corticosteroids or with biologic therapy had to be discontinued at least 30 days before baseline (Day 1), and topical corticosteroids were tapered and discontinued by Day 1. Systemic corticosteroids in the form of oral prednisone or equivalent to a maximum dose of 1 mg/kg/day were allowed only for subjects already receiving them before baseline. From Day 1, the corticosteroid dose was tapered according to the following protocol:

- Reduce by 10 mg every week until reaching a dose of 40 mg/day;
- then reduce by 5 mg every week until reaching a dose of 20 mg/day;
- then reduce by 2.5 mg every week until reaching 0 mg/day.

The study investigator could amend this suggested schedule, if necessary, in consultation with the medical monitor of the study.

**Assessments**

Subjects underwent slit-lamp biomicroscopy at each study visit to evaluate eye structures and VH. Severity of VH was categorized using a modified Standardization of Uveitis Nomenclature scale that.
Pharmaceuticals and Medical Devices Agency.

With the intent-to-treat principle, all randomized subjects comprised the primary population for efficacy analyses. For the primary analyses of all VH response end points, subjects rescued before Month 5 were treated as nonresponders. For subjects not rescued before Month 5, missing VH data at Month 5 were imputed using the last observation carried forward approach. For the sensitivity analyses, a per-protocol population was used, which consisted of the intent-to-treat population excluding subjects with significant protocol violations or missing a Month 5 VH score. For the assessment of corticosteroid tapering success, the analysis included all subjects who were taking systemic corticosteroid(s) at baseline with an overall prednisone-equivalent dose $>5$ mg/day (intent-to-taper population). Subjects rescued before Month 5 were treated as tapering failures. For subjects not rescued before Month 5, missing data on the overall prednisone-equivalent dose at Month 5 were imputed using the last observation carried forward.

The primary efficacy end point and binary secondary end points were analyzed using the Fisher exact test. The Hochberg step-up procedure was used to control the overall type 1 error rate associated with 2 treatment comparisons for the primary efficacy end point. The continuous secondary efficacy variables’ changes from baseline in VH and BCVA were assessed using a mixed-effects model for repeated measures with baseline score as a covariate; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as the random effect. Statistical testing of efficacy end points was conducted at a significance level of 0.05 (2-sided). Safety measures were summarized descriptively for the safety population, which comprised all randomized subjects who received $\geq 1$ dose of study drug.

### Study Oversight

An ethics committee or institutional review board at each participating site reviewed and approved the clinical study protocol, informed consent form, and all other appropriate study-related documents. The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Study sites in the United States complied with the provisions of the Health Insurance Portability and Accountability Act. Before undergoing any study-related activity or administration of study medication, subjects were required to understand and sign the informed consent form.

The SAKURA Study included a data monitoring committee that met periodically to conduct an independent review of unmasked aggregated and individual-level data related to study safety, data integrity, and overall study conduct. In addition, a study steering committee was established that consisted of key investigators. Throughout the course of SAKURA Study 1, members of the steering committee led discussions with study investigators, coordinators, and staff on issues concerning patient recruitment and retention, protocol amendments, adverse events, and other aspects related to the study.

### Results

#### Subject Disposition

A total of 347 subjects (348 study eyes) were randomized at 103 sites in the European Union, India, Israel, Japan, Latin America, and the United States from May 31, 2011, to March 31, 2013 (Fig 2). One subject was inadvertently enrolled twice and was...

---

**Figure 1.** Sirolimus study Assessing double-masked Uveitis TreAtment (SAKURA) Study 1 design. IVT = intravitreal.
randomized to receive the 880-μg dose each time. The second identification number was excluded from the efficacy analyses. The safety population included all randomized subject identification numbers, excluding 2 subjects who were randomized but not treated, yielding a safety population of 346 study eyes. A total of 69 subjects (19.9%) who were receiving systemic corticosteroid(s) in a prednisone-equivalent dose of ≥7.5 mg/day at baseline comprised the intent-to-taper population.

The database of SAKURA Study 1 was locked on April 22, 2015, after completion of the open-label treatment phase; data from this phase of the study will be reported at a later date.

**Baseline Demographics and Clinical Characteristics**

Baseline characteristics are shown in Table 2. A majority of subjects (88.8%) had a VH score of 1.5+ (36.9%) or 2+ (51.9%). Bilateral uveitis was identified in 66.6% of subjects, with more than three fourths of subjects (77.8%) having an unknown underlying cause of uveitis in the study eye (i.e., idiopathic or undifferentiated) (Table S3, available at www.aaojournal.org). Specific investigator-reported diagnoses at baseline included sarcoidosis (8.4%), Vogt–Koyanagi–Harada syndrome (5.2%), and birdshot chorioretinopathy (2.6%). The distribution of subjects based on anatomic location in the study eye was intermediate (34.0%), posterior (34.0%), and panuveitis (32.0%). Baseline characteristics were balanced among the 3 dose groups, except for the mean duration of active uveitis in the study eye (55.8 months with 44 μg, 38.8 months with 440 μg, and 48.6 months with 880 μg). The reported ocular comorbidities in the study eye included cataract (24.8%), cystoid macular edema (15.9%), glaucoma (9.8%), iridocyclitis (8.9%), macular fibrosis (7.8%), and vitreous detachment (7.2%).

**Efficacy Outcomes**

A higher proportion of subjects in the 440 μg dose group (22.8%) achieved the primary end point of VH = 0 than in the 880 μg (16.4%) and 44 μg (10.3%) dose groups (P = 0.025 for 440 versus 44 μg; P = 0.182 for 880 versus 44 μg; adjusted for multiplicity) (Fig 3). Likewise, a higher proportion of subjects in the 440 μg dose group (52.6%) achieved the key secondary end point of VH = 0 or 0.5+ than in the 880 μg (43.1%) and 44 μg (35%) dose groups (P = 0.008 for 440 versus 44 μg; P = 0.228 for 880 versus 44 μg). Clinical outcomes improved as early as the first analysis visit at Week 2 and continued through Month 5 (Fig 4). The proportion of subjects with a VH score of 0 or a 2-unit improvement at Month 5 was 28.1% in the 440 μg group, 19.0% in the 880 μg group, and 16.2% in the 44 μg group (P = 0.039 for 440 versus 44 μg; P = 0.610 for 880 versus 44 μg). No inferential treatment comparisons were conducted between the 440 and 880 μg dose groups. Results for all outcomes were similar in the sensitivity analyses conducted for the per-protocol population (data not shown).

A total of 217 subjects had a diagnosis of NIU of the posterior segment without concomitant anterior segment inflammation (i.e., all subjects with anterior uveitis or panuveitis were excluded). The proportion of these subjects who achieved VH of 0 in the 440 μg dose group (30.0%) was significantly higher (P = 0.0016) than in the 44 μg group (9.2%) and did not differ between the 880 μg (16.9%) and 44 μg (P = 0.220). There was no significant association between achieving a VH = 0 outcome and the interaction of anterior segment inflammation and treatment (P = 0.064). There was a significant association with treatment (440 versus 44 μg), however, suggesting that a treatment dose of 440 μg was more effective in reducing ocular inflammation irrespective of whether a subject had any anterior segment inflammation (P = 0.0099). This was consistent with the primary results. Further, higher proportions of subjects in the 440 μg (60.0%; P = 0.002) and 880 μg (46.5%; P = 0.128) groups achieved a VH score of 0 or 0.5+ than in the 44 μg group (32.9%).

The mean changes in VH from baseline to Month 6 demonstrated sustained improvement in all intravitreal sirolimus dose groups. The proportions of subjects with a VH score of 0 at Month 6 were 21.9% with 440 μg, 12.9% with 880 μg, and 12.0% with 44 μg (all P > 0.05).

![Figure 2. Subject disposition. *Two screen failure subjects who were randomized but not treated were excluded from the safety population. **One subject was inadvertently enrolled twice and randomized to receive the 880 μg dose regimen each time, with 2 different subject identification numbers, each assigned to a different study eye. The safety data from both identification numbers were included in safety analyses, whereas the efficacy data from the second identification number were excluded from the efficacy analyses. ITT = intent to treat; IVT = intravitreal.](image-url)
Visual acuity was preserved over time in each dose group (Fig 5). Overall, 80.4%, 80.0%, and 79.0% of subjects in the 440, 880, and 44 μg dose groups, respectively, maintained or improved their baseline BCVA at Month 5 (i.e., experienced a gain in BCVA, no change in BCVA, or lost <5 letters). In a post hoc subgroup logistic regression analysis of treatment (440 or 44 μg) and baseline BCVA (<50 or ≥50 letters), there were no significant associations of the interaction term (treatment dose × BCVA) on the VH score of 0 (P > 0.05), indicating that subjects in the 440 μg group with a low BCVA at baseline were more likely to improve in score at Month 5. Subjects with a baseline BCVA <20/100 in the 44 μg group demonstrated an average gain of 10.5 letters at Month 5 (Fig 6).

Of the 69 subjects included in the intent-to-tape population, 48 (69.6%) were successfully tapered, and 47 of the 48 subjects were completely tapered off corticosteroids. The proportions of tapering successes were 76.9% (20/26) in the 440 μg group, 66.7% (14/21) in the 880 μg group, and 63.6% (14/22) in the 44 μg dose group. Among subjects achieving a VH score of 0 or 0.5+ (46.2%) in the 440 μg group, 33.3% in the 880 μg group, and 27.3% in the 44 μg dose group were tapered to a prednisone-equivalent dose of ≤5 mg/day of corticosteroids. Among subjects with VH = 0, 26.9% (7/26) in the 440 μg group were successfully tapered, whereas none of the 22 subjects (0%) in the 44 μg dose group could be successfully tapered (P = 0.0113).

A total of 99 subjects (33, 29, and 37 in the 44, 440, and 880 μg groups, respectively) presented with a CRT 26.9% (7/26) in the 440 μg dose group were tapered to a prednisone-equivalent dose of 50 letters (69.6%) were successfully tapered, and 47 of the 48 subjects were tapered at Month 5 in the 440, 880, and 44 μg dose groups, respectively.

The incidence of serious ocular adverse events was 20.5% in the 880 μg dose group, 18.8% in the 440 μg group, and 16.2% in the 44 μg dose group (Table S5, available at www.aaojournal.org). The incidence rates of specific serious ocular adverse events in the study eye that were potentially related to the study drug (in the 44, 440, and 880 μg groups, respectively) were 0%, 0.9%, and 3.4% for sterile endophthalmitis, and 0.9%, 1.8%, and 1.7% for medication residue (from the presence of drug depot in the visual axis). Although there were no instances of confirmed culture-positive endophthalmitis, a single case of endophthalmitis was reported in the 880 μg dose group during the double-masked treatment period. The event resolved with therapy. Glaucoma was reported as a serious adverse event in 1 subject each in the 44 and 440 μg groups.

The most common nonocular adverse events (reported in >3% of subjects overall) were nasopharyngitis (3.2%) and headache (4.6%), but neither was considered related to the study drug. Overall, there were no clinically important changes in laboratory parameters or vital signs, suggesting a negligible or undetectable systemic activity after intravitreal sirolimus injection in the study subjects.

Similar to the study eye, the most common adverse events in the fellow eye were related to ocular inflammation, specifically iridocyclitis and uveitis, both of which occurred in 5.8% of subjects. No adverse events in the fellow eye were considered related to the study drug.

Five subjects (1.4%) discontinued the study before Month 5 because of adverse events, including 3 subjects in the 44 μg group (1 because of a foreign body in the eye, 1 because of retinal infiltrates, and 1 because of increased IOP) and 2 subjects in the 880 μg group (both because of uveitis). A death (due to stroke) occurred in 1 subject in the 44 μg dose group; the event was considered unrelated to the study drug.

**Discussion**

In the SAKURA Study 1, every-other-month injections of intravitreal sirolimus 440 μg demonstrated significant improvements in reducing ocular inflammation in subjects with active NIU of the posterior segment (i.e., posterior, intermediate, or panuveitis) compared with an active control dose of 44 μg. In a heterogeneous population of subjects (15 countries and 103 clinical sites), significantly more subjects with NIU of the posterior segment (~23%) achieved a complete resolution of inflammation (VH = 0) with the 440 μg dose when compared with the 44 μg dose. At Month 5, more than 50% of subjects in the 440 μg group experienced a statistically significant reduction in inflammation from an average VH score of 2+ to 0 or 0.5+ (no or minimal inflammation). A between-treatment comparison clearly established the superiority of the 440 μg dose to the 44 μg dose (active comparator). The response to the 880 μg intravitreal dose was numerically superior, yet not statistically different from the 44 μg dose at all time points up to Month 5. The reported results of the SAKURA Study 1, the first randomized, controlled, multicenter, multinational trial of intravitreal sirolimus, demonstrate the efficacy and safety of this therapy for NIU of the posterior segment.

The baseline difference in the duration of uveitis among the 3 treatment groups was not clinically relevant for 2 reasons. First, only subjects with active uveitis were enrolled in the study.
and disease duration may not correlate with disease severity. Although there was a significant interaction effect of duration of uveitis at baseline and treatment on VH of 0, this result was driven by a few subjects who had uveitis for a long duration. Second, the logistic regression including duration of uveitis revealed treatment (dose of intravitreal sirolimus) to be the only main effect that was significantly associated with response (VH = 0), thus confirming that treatment with 440 μg of intravitreal sirolimus had a more marked effect on the ability to achieve a VH of 0.

Apart from an improved VH, the 440 μg dose of intravitreal sirolimus also showed preservation of BCVA to Month 5. Given the lack of a significant interaction effect between treatment and BCVA (P > 0.05), and a numerically greater treatment effect, it appears that the 440 μg dose had a propensity to maintain the BCVA of subjects who had good vision at baseline and improve it in subjects who had a lower BCVA at the time of recruitment into the study.

The intravitreal sirolimus 440 μg group also had the highest proportion of subjects with successful tapering of corticosteroid dose (to ≤5 mg/day of prednisone or

Table 2. Baseline Demographics and Clinical Characteristics (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th></th>
<th>44 μg (n = 117)</th>
<th>440 μg (n = 114)</th>
<th>880 μg (n = 116)</th>
<th>Overall (N = 347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization (year) Mean (SD)</td>
<td>45.7 (14.97)</td>
<td>46.5 (14.48)</td>
<td>47.4 (14.08)</td>
<td>46.5 (14.48)</td>
</tr>
<tr>
<td>Median</td>
<td>46.10</td>
<td>47.10</td>
<td>48.45</td>
<td>47.40</td>
</tr>
<tr>
<td>Min, Max</td>
<td>18.4, 83.6</td>
<td>18.1, 78.3</td>
<td>18.9, 74.3</td>
<td>18.1, 83.6</td>
</tr>
<tr>
<td>Age group (year) &lt;65</td>
<td>104 (88.9%)</td>
<td>103 (90.4%)</td>
<td>99 (85.3%)</td>
<td>306 (88.2%)</td>
</tr>
<tr>
<td>≥65</td>
<td>13 (11.1%)</td>
<td>11 (9.6%)</td>
<td>17 (14.7%)</td>
<td>41 (11.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (55.6%)</td>
<td>68 (59.6%)</td>
<td>75 (64.7%)</td>
<td>208 (59.9%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>54 (46.2%)</td>
<td>55 (48.2%)</td>
<td>55 (47.4%)</td>
<td>164 (47.3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>44 (37.6%)</td>
<td>43 (37.7%)</td>
<td>45 (38.8%)</td>
<td>132 (38.0%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>8 (6.8%)</td>
<td>8 (7.0%)</td>
<td>8 (6.9%)</td>
<td>24 (6.9%)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>8 (6.8%)</td>
<td>8 (7.0%)</td>
<td>8 (6.9%)</td>
<td>24 (6.9%)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0%</td>
<td>1 (0.9%)</td>
<td>0%</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>6 (5.1%)</td>
<td>4 (3.5%)</td>
<td>2 (1.7%)</td>
<td>11 (3.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (5.1%)</td>
<td>5 (4.3%)</td>
<td>6 (5.1%)</td>
<td>12 (3.5%)</td>
</tr>
<tr>
<td>Baseline VH score of study eye Mean (SD)</td>
<td>1.94 (0.503)</td>
<td>1.91 (0.442)</td>
<td>1.95 (0.484)</td>
<td>1.94 (0.477)</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.5+</td>
<td>43 (36.8%)</td>
<td>44 (38.6%)</td>
<td>41 (35.3%)</td>
<td>128 (36.9%)</td>
</tr>
<tr>
<td>2+</td>
<td>61 (52.1%)</td>
<td>58 (50.9%)</td>
<td>61 (52.6%)</td>
<td>180 (51.9%)</td>
</tr>
<tr>
<td>3+ or 4+</td>
<td>13 (11.1%)</td>
<td>12 (10.5%)</td>
<td>14 (12.1%)</td>
<td>39 (11.2%)</td>
</tr>
<tr>
<td>Bilateral uveitis</td>
<td>75 (64.1%)</td>
<td>78 (68.4%)</td>
<td>78 (67.2%)</td>
<td>231 (66.6%)</td>
</tr>
<tr>
<td>Anatomic location of uveitis in study eye* Intermediate</td>
<td>43 (36.8%)</td>
<td>37 (32.5%)</td>
<td>38 (32.8%)</td>
<td>118 (34.0%)</td>
</tr>
<tr>
<td>Posterior</td>
<td>37 (31.6%)</td>
<td>42 (36.8%)</td>
<td>39 (33.6%)</td>
<td>118 (34.0%)</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>37 (31.6%)</td>
<td>35 (30.7%)</td>
<td>39 (33.6%)</td>
<td>111 (32.0%)</td>
</tr>
<tr>
<td>Months since first diagnosis of uveitis (study eye)† Mean (SD)</td>
<td>55.8 (74.61)</td>
<td>38.8 (47.28)</td>
<td>48.6 (66.30)</td>
<td>47.8 (64.07)</td>
</tr>
<tr>
<td>Median</td>
<td>29.5</td>
<td>21.8</td>
<td>25.8</td>
<td>26.2</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.2, 411.7</td>
<td>0.3, 212.4</td>
<td>0.1, 346.6</td>
<td>0.1, 411.7</td>
</tr>
<tr>
<td>Baseline BCVA of study eye (letters) Mean (SD)</td>
<td>63.6 (16.76)</td>
<td>67.7 (14.24)</td>
<td>64.6 (16.30)</td>
<td>65.3 (15.87)</td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
<td>70</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Min, Max</td>
<td>5.0, 92.0</td>
<td>3.0, 95.0</td>
<td>3.0, 90.0</td>
<td>3.0, 95.0</td>
</tr>
<tr>
<td>Overall prednisone-equivalent dose (intent-to-taper population)‡ Number of subjects</td>
<td>22</td>
<td>26</td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.9 (14.47)</td>
<td>22.9 (13.85)</td>
<td>18.9 (10.36)</td>
<td>22.0 (13.08)</td>
</tr>
<tr>
<td>Median</td>
<td>20.0</td>
<td>18.8</td>
<td>17.5</td>
<td>20.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>7.5, 60.0</td>
<td>7.5, 50.0</td>
<td>7.5, 40.0</td>
<td>7.5, 60.0</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; Max = maximum; Min = minimum; SD = standard deviation; VH = vitreous haze.

The distribution of racial and ethnic groups was similar across the study arms.

*Subjects with both posterior uveitis and panuveitis in the study eye at baseline were mapped to the “posterior” category.

†The duration of uveitis (months) was derived as [Day 1 visit date – uveitis onset date (observed or imputed)]/30.

‡The intent-to-taper population comprised all subjects who were taking systemic corticosteroid(s) at Day 1 (baseline) with an overall prednisone-equivalent dose >5 mg/day.

2418
equivalent) by Month 5. Although the results were not statistically significant because of the small sample size, the discernable corticosteroid-sparing effect observed with the 440 μg dose is important to note in light of its potential to reduce the known complications associated with chronic systemic corticosteroid therapy even at a low dose (≤7.5 mg/day).

Subjects enrolled in the SAKURA Study 1 discontinued the use of biologics and non-corticosteroid immunosuppressants before the first intravitreal sirolimus injection at baseline. Thus, the positive outcomes observed in the study were achieved in subjects receiving monotherapy with intravitreal sirolimus during the major portion of the study period. The majority of subjects in each dose group did not require rescue therapy during the study, supporting the efficacy of sirolimus in reducing ocular inflammation. Furthermore, the results suggest that inhibition of the mTOR pathway with local sirolimus injections can effectively resolve ocular inflammation in subjects with NIU of the posterior segment without concomitant use of other local or systemic immunoregulators.

The overall incidence of ocular and nonocular adverse events was similar across the 3 dose groups. There was a slight dose-dependent trend in the proportion of subjects

---

**Figure 3.** Vitreous haze (VH) outcomes. *P* values are for comparisons versus 44 μg. *Adjusted for multiplicity.

---

**Figure 4.** Vitreous haze 0 or 0.5+ response rate, by analysis visit. *P* < 0.01 versus 44 μg. †*P* < 0.05 versus 44 μg. Other comparisons versus 44 μg were nonsignificant.
reporting any ocular adverse event (worsened ocular inflammation, predominantly panuveitis; MedDRA preferred term “uveitis”). Uveitis as an adverse event (e.g., intermediate, posterior, or panuveitis) was likely due to underlying disease progression. Iridocyclitis was the most common ocular adverse event in the study eye and was not unexpected, given subjects with uveitis involving the anterior segment were eligible for the study and were tapered from their topical medications before Day 1. Presence of medication residue could have been influenced by the injection technique (i.e., toward the center of the vitreous directly into the visual axis) or factors such as subject position and vitreous consistency. Findings of serious ocular or serious nonocular adverse events potentially related to the study drug or injection procedure were consistent with the results of an earlier study of intravitreal sirolimus26,27 and did not include any unexpected safety concerns. Of note, intravitreal sirolimus was associated with a low incidence of

Figure 5. Best-corrected visual acuity (BCVA) Early Treatment of Diabetic Retinopathy Study (ETDRS) letters by analysis visit. P values are for comparison versus 44 μg. Other comparisons versus 44 μg were nonsignificant. Bars represent standard error. BL = baseline; SE = standard error; Wk = week.

Figure 6. Median change in best-corrected visual acuity (BCVA) Early Treatment of Diabetic Retinopathy Study (ETDRS) letters from baseline at Month 5. Observed cases. Statistical analysis was not performed.
the types of ocular adverse events common in subjects receiving intraocular corticosteroids (e.g., cataract, glaucoma, and increased IOP).\textsuperscript{17,18} Nonocular adverse events commonly seen with the systemic administration of sirolimus, such as hyperlipidemia and anemia,\textsuperscript{29} were absent in SAKURA Study 1, suggesting the activity of intravitreal sirolimus is local to the eye, with negligible systemic bioactivity.

The intravitreal sirolimus 440 \textmu g dose exhibited the best risk-to-benefit ratio in this study, demonstrating greater efficacy than either of the other doses and a numerically lower incidence of adverse events related to ocular inflammation than the 880 \textmu g dose. This particular dose-response curve was unexpected, yet consistent in that the 440 \textmu g dose showed greater efficacy than the 880 \textmu g dose at every double-masked assessment interval up to the Month 5 efficacy end point. Other ocular drugs (latanoprost, pegaptanib, aflibercept, and ranibizumab) have shown similar dose-response curves, wherein higher doses of the drugs demonstrated similar or worse efficacy compared with lower doses, in line with the concept of hormesis.\textsuperscript{30–33}

This study enrolled a heterogeneous, multinational population with a spectrum of intermediate, posterior, and panuveitis. It is noteworthy that in the subgroup of subjects without anterior segment involvement (a population similar to that enrolled in the HURON [cHronic Uveitis: evaluation of the intRaVitreal dexamethasOn implant] trial in which subjects received an intravitreal dexamethasone implant),\textsuperscript{18} 60% of subjects in the 440 \textmu g dose group achieved a VH score of 0 or 0.5+ at Month 5 compared with 33% in the 440 \textmu g dose group overall (\textit{P} = 0.0015). The numerically higher percentage of responders among subjects without anterior segment involvement could, in part, be due to the rapid topical corticosteroid tapering schedule.

**Study Limitations**

One limitation of this study was that a minimally active dose of intravitreal sirolimus (44 \textmu g) was used as an active comparator in place of placebo. The lack of a true placebo arm could have underestimated the actual treatment effect of the 440 \textmu g dose; however, the consistent results through various subgroup analyses provide clear evidence for the efficacy of the 440 \textmu g dose. The population used to ascertain corticosteroid tapering success was small because most of the enrolled subjects were corticosteroid free at randomization, limiting statistical analysis to assess the

---

**Table 4. Ocular Adverse Events in the Study Eye (>5% of Subjects in Any Dose Group)**

<table>
<thead>
<tr>
<th>Type (Preferred Term)</th>
<th>44 \textmu g (n = 117)</th>
<th>440 \textmu g (n = 112)</th>
<th>880 \textmu g (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iridocyclitis</td>
<td>23 (19.7%)</td>
<td>21 (18.8%)</td>
<td>22 (18.8%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>18 (15.4%)</td>
<td>17 (15.2%)</td>
<td>20 (17.1%)</td>
</tr>
<tr>
<td>Uveitis\textsuperscript{a}</td>
<td>11 (9.4%)</td>
<td>16 (14.3%)</td>
<td>26 (22.2%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>9 (7.7%)</td>
<td>13 (11.6%)</td>
<td>14 (12.0%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>10 (8.5%)</td>
<td>8 (7.1%)</td>
<td>6 (5.1%)</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>12 (10.3%)</td>
<td>7 (6.3%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>6 (5.1%)</td>
<td>5 (4.5%)</td>
<td>8 (6.8%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>10 (8.5%)</td>
<td>4 (3.6%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>3 (2.6%)</td>
<td>3 (2.7%)</td>
<td>9 (7.7%)</td>
</tr>
<tr>
<td>Macular edema</td>
<td>1 (0.9%)</td>
<td>7 (6.3%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td>Iris adhesions</td>
<td>1 (0.9%)</td>
<td>7 (6.3%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>Cataract subcapsular</td>
<td>(0%)</td>
<td>4 (3.6%)</td>
<td>6 (5.1%)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP increased</td>
<td>20 (17.1%)</td>
<td>18 (16.1%)</td>
<td>20 (17.1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication residue\textsuperscript{b}</td>
<td>1 (0.9%)</td>
<td>7 (6.3%)</td>
<td>7 (6.0%)</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure.

Adverse events are per subject.

\textsuperscript{a}MedDRA preferred term “uveitis,” and lower level terms “panuveitis,” “pars planitis,” and “uveitis.”

\textsuperscript{b}MedDRA preferred term “choroiditis.”

\textsuperscript{c}Transient drug depot in the visual axis.
differences in favor of the 440 µg dose. In addition, the lack of predefined criteria for determining the presence of macular edema precluded the statistical assessment of treatment effects on this parameter.

In summary, the results of the SAKURA Study 1 demonstrated 5-month improvement in VH combined with preservation of BCVA and reduction in corticosteroid treatment burden in patients with active NIU of the posterior segment who received repeated intravitreal injections of sirolimus 440 µg. There were no clinically relevant systemic safety issues and there was a low incidence of adverse events typically associated with corticosteroid therapy. The data provide level 1 evidence supporting the strategy of mTOR inhibition in NIU of the posterior segment using a locally administered therapy. Future research on intravitreal sirolimus will likely explore its potential role in combination therapy regimens, its corticosteroid-sparing efficacy in a larger population, and its longer-term safety and efficacy (currently being evaluated in the open-label treatment phase of the SAKURA Study 1).

Acknowledgments. The authors acknowledge the important intellectual contributions to the article from Dr. Yusuf Ali, Dr. Vincent Baeyens, Dr. Masaaki Kageyama, Dr. Sri Mudumba, Dr. Michelle Chernock, Dr. Kavitha Damal (all employees of Santen, Inc.), and Mary Ellen Valentine (previous employee of Santen, Inc.). The authors also thank the members of the SAKURA Data Monitoring Committee (Dr. Henry J. Kaplan of the Kentucky Lions Eye Center, University of Louisville, Kentucky; Dr. Jennifer Lim of the Illinois Eye and Ear Infirmary, University of Illinois College of Medicine at Chicago; and Dr. H. Nida Sen of the National Eye Institute, National Institutes of Health, Bethesda, MD) for their work on the trial, especially Dr. Kaplan for his review of the manuscript. The authors received writing assistance in preparation of the initial manuscript draft from Dr. Andrew Horgan and editorial assistance in draft revisions from Harold Schombert, both employees of BioScience Communications (New York, NY). These contributions were funded by Santen, Inc.

References

Footnotes and Financial Disclosures

Originally received: February 2, 2016.
Final revision: July 19, 2016.
Accepted: July 20, 2016.

A list of the members of the Sirolimus study Assessing double-masked Uveitis tReAtment (SAKURA) study group is available online (www.aaojournal.org).

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; CRT = central retinal thickness; IOP = intraocular pressure; mTOR = mammalian target of rapamycin; NEI VFQ-25 = 25-item National Eye Institute Visual Function Questionnaire; NIU = noninfectious uveitis; OCT = optical coherence tomography; SAKURA = Sirolimus study Assessing double-masked Uveitis tReAtment; SAVE = Sirolimus as a therapeutic Approach for uVEitIs study; VH = vitreous haze.

Correspondence:
Quan Dong Nguyen, MD, MSc, 3902 Leavenworth Street, Omaha, NE 68198. E-mail: quan.nguyen@umcn.edu.